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NEPHROLOGY FORUM

Oncogenic hypophosphatemic osteomalacia

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Case presentation

A 56-year-old black woman was admitted to the Hospital of the University of Pennsylvania for reevaluation of diffuse bone pain and muscle weakness. She had been in good health until 5 years prior to admission, when she developed a diffuse aching pain in her chest and extremities. Three years before admission, she complained of increasing muscle weakness, worsening hip pain, and thoracic pain and discomfort accentuated by respiration. Family history was negative for bone or renal disease.

Laboratory evaluation revealed normal BUN, creatinine, uric acid, and serum electrolyte levels, an elevated alkaline phosphatase of 750 IU, serum calcium ranging between 9.0 and 9.4 mg/dl, and serum phosphate between 1.0 and 1.8 mg/dl. Total protein was 7.8 g/dl, with a serum albumin of 3.5 g/dl. Urine pH ranged between 5.0 and 5.5, and a urine screen for amino acids was normal except for increased 24-hr excretion of hydroxyproline. Serum PTH was normal, and plasma $1,25(OH)_2D_3$ was 56 pmol/liter (normal, 89 ± 25). A 24-hour urine collection contained 1150 mg of creatinine, 179 mg of calcium, and 540 mg of phosphate, at a time when serum phosphate was 1.3 mg/dl and the serum creatinine was 1.0 mg/dl; the fractional phosphate excretion was 33%. A bone survey revealed extensive demineralization, multiple rib fractures, and fractures of the right superior and left inferior pubic rami without callus formation. The urine was negative for Bence Jones protein. Biopsy of the posterior iliac crest revealed osteomalacia. A 72-hour stool fat collection revealed less than 1.5 g/day, and a jejunal biopsy was normal. Intravenous pyelogram, an upper and lower gastointestinal series, liver scan, bone marrow aspiration, and mammography all were normal.

The patient was treated over the next several years with various combinations of oral phosphate, calcium, and vitamin D. On a regimen of 2.5 g/day of elemental phosphorus, 2 g/day of calcium carbonate, and 50,000 units of vitamin D every other day, the serum phosphate ranged between 2.2 and 2.8 mg/dl, and the serum calcium fluctuated between 9.5 and 10.5 mg/dl. She continued to complain of diffuse bone pain and muscle weakness and subsequently was treated with 1 μg/day of 1 αOH vitamin D and 3 g/day of elemental phosphorus. On this regimen, the serum phosphate varied between 1.8 and 2.1 mg/dl, the serum calcium level ranged between 8.2 and 8.6 mg/dl, and the PTH increased from 9 to 12 μlEq/ml. Treatment with calcium carbonate was reinstituted, but after 6 months of therapy the patient was readmitted for evaluation because of continuing bone pain.

On admission, she complained of new discomfort and pressure in the left plantar area. The blood pressure was 140/86 mm Hg; pulse, 72; and weight, 186 lbs. Funduscopic examination showed minimal arteriolar narrowing, sharp discs, and no hemorrhages or exudates. The rib cage was diffusely tender to palpation. Examination of the heart and lungs was normal. Neither hepatosplenomegaly nor costovertebral angle tenderness was present. There was a firm, slightly tender, small nodule barely palpable in the sole of the left foot.

The BUN was 12 mg/dl and the serum creatinine was 1.1 mg/dl. Blood chemistry studies revealed: sodium, 136 mEq/liter; potassium, 3.6, mEq/liter; chloride, 104 mEq/liter; and bicarbonate, 27 mEq/liter. Serum calcium was 9.5 mg/dl, and phosphate was 2.3 mg/dl, with a fractional phosphate excretion of 58%. Serum protein was 7.6 g/dl; serum albumin was 3.8 g/dl. Urinalysis showed a pH of 5.0; a specific gravity of 1.014; and no protein, glucose, cells, or casts. Alkaline phosphatase was 620 IU/liter; serum $1,25(OH)_2D_3$, 111 pmol/liter; and PTH, 7 μlEq/ml.

Chest x-ray revealed multiple rib fractures. The heart was normal in size and the lung fields were clear. A blood-pool study of the left leg with ^{99}Tc-labeled albumin revealed a vascular tumor of the left foot, and left femoral arteriography demonstrated an extensive lesion in the region of the proximal metatarsal bones with involvement of the skin of the proximal half of the foot.

Biopsy of the involved area revealed a sclerosing hemangioma; a below-the-knee amputation was performed. Following surgery, the serum phosphate level rose within 48 hours to 4.1 mg/dl, and the fractional phosphate excretion fell to 16%. Six months later the patient was well and had no bone pain; x-ray films of the pelvis revealed almost complete healing of the fractures of the pubic rami. Four years later, serum calcium was 9.3 mg/dl; serum phosphate, 4.8 mg/dl; and alkaline phosphatase, 87 IU/liter.

Discussion

DR. ZALMAN S. AGUS (*Associate Professor of Medicine, University of Pennsylvania School of Medicine, and Chief, Renal-Electrolyte Section, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania*): This patient, previously in good health, experienced at age 48 marked hypophosphatemia, low levels of $1,25(OH)_2D_3$, renal phosphate wasting, and symptomatic bone disease in the presence of normocalcemia

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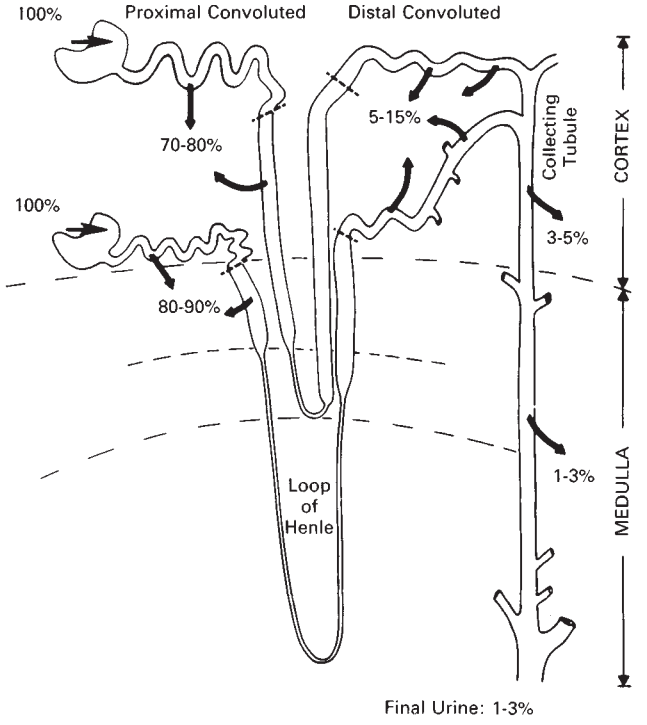

Fig. 1. *Sites of phosphate transport along the mammalian nephron in the absence of PTH.* (© 1983, the Williams & Wilkins Co., Baltimore, in prep.)

and normal levels of PTH. Large doses of phosphate and supraphysiologic doses of 1α-vitamin D did not alleviate her disease, but the removal of a sclerosing hemangioma immediately resolved all symptoms. The patient thus illustrates acquired vitamin D-resistant rickets due to tumor-induced or so-called oncogenic osteomalacia. Before discussing the pathogenesis and therapy of vitamin D-resistant rickets, I would like to review some of the current concepts concerning the interrelationship between renal phosphate transport and vitamin D metabolism.

Renal phosphate transport

Sites of transport. Our knowledge of the sites of phosphate transport within the nephron, the factors that alter transport, and the mechanisms by which transport takes place has been expanded considerably in the last decade by data obtained by micropuncture, isolated nephron segment perfusion studies, and studies of membrane vesicles [1, 2]. Phosphate transport occurs throughout the nephron, except in the loop of Henle. Figure 1 represents a composite view of transport sites in the mammalian nephron in the absence of increased levels of parathyroid hormone [3]. Phosphate is transported in all segments of the proximal tubule, but the rate of transport per unit length seems to diminish along the tubule and is higher in the convoluted segment than in the straight segment. Because juxtamedullary nephrons have a longer convoluted segment than do superficial nephrons, fractional reabsorption of the filtered phosphate load is higher, and therefore fractional delivery into the thin descending limb of Henle's loop is less in deeper than in superficial nephrons. No net phosphate transport occurs in the thin descending, thin ascending, and thick ascending limbs of Henle's loop. A small fraction of the filtered load is reabsorbed in the distal convoluted tubule, and a much smaller component is reabsorbed in the cortical collecting tubule and medullary collecting duct. Transport beyond the distal tubule is not altered by the factors that normally regulate phosphate homeostasis, and transport here is driven by purely passive forces such as voltage, tubular flow, and concentration gradients.

Table 1. Factors that alter urinary phosphate excretion

Plasma phosphate concentration
Dietary phosphate intake
Proximal tubular sodium reabsorption
Extracellular fluid volume
Acetazolamide
Hormones
Parathyroid hormone
Growth hormone
Thyrocalcitonin
Insulin
$1,25(OH)_2D_3$ (?)
Acid-base balance
Plasma glucose concentration
Serum calcium concentration

Factors altering phosphate transport. Table 1 lists some of the many factors that alter renal phosphate transport and excretion [1]. Studies in experimental animals have shown that increases in PCO_2, filtered glucose load, and hypercalcemia diminish tubular phosphate transport and increase phosphate excretion, whereas hyperinsulinemia and chronic administration of growth hormone stimulate phosphate transport [1]. The role of vitamin D and its metabolites remains controversial and will be discussed subsequently. In terms of day-to-day homeostatic regulation of phosphate balance, however, two factors are most important: plasma levels of circulating PTH and dietary phosphate intake.

Parathyroid hormone, via stimulation of adenylate cyclase activity, inhibits transport in the proximal convoluted tubule, pars recta, and distal convoluted tubule. In the presence of normal plasma levels of PTH, distal phosphate transport is inhibited, and the bulk of renal phosphate transport occurs within the proximal tubule. In the absence of parathyroid hormone, transport capacity is increased in both segments and leads to an increased transport maximum (Tm) for phosphate, and thus hyperphosphatemia.

In recent years, it has become clear that dietary phosphate intake is a powerful regulator of phosphate excretion. Studies in humans and experimental animals show a significant fall in phosphate excretion within the first 24 hours of phosphate deprivation, and virtual elimination of phosphate from the urine within 72 hours [4, 5]. As shown in Figure 2, this renal adaptation limits, but does not prevent, phosphate depletion following dietary phosphate deprivation because of continued gastrointestinal phosphate secretion and phosphate loss in the stool [4]. Although not well understood, the mechanism of this adaptation is not a function of the fall in serum phosphate or of a reduction in PTH secretion. Thus although both of these events occur and may contribute to the fall in phosphate excretion, other unknown factors seem to be more important. In fact, in the animal adapted to phosphate deprivation, neither acute

elevation of the filtered load nor infusion of PTH produces a significant change in phosphate excretion [6, 7].

Cellular mechanisms of transport. The study of vesicles prepared from renal brush-border membranes has generated new concepts of phosphate transport [2]. Figure 3 illustrates a current working model for phosphate transport. Vesicle studies indicate that an active sodium-dependent phosphate uptake mechanism is present at the brush border [8, 9]. This cotransport process, which occurs against an electrochemical gradient for phosphate, is secondarily active, in effect being fueled by the energy utilized in maintaining the transmembrane sodium gradient, which allows inward diffusion of sodium and phosphate. Direct measurements are lacking, but using measurements in other tissues, researchers have assumed that the intracellular inorganic phosphate concentration approximates that in the extracellular fluid. In combination with a favorable electrical gradient, this concentration allows for passive exit of phosphate at the contraluminal membrane. Consistent with this hypothesis is the demonstration that phosphate transport across the basolateral membrane of the renal tubular cell is sodium independent [9].

This model allows for modulation of net phosphate transport in several ways. First, phosphate transport can be inhibited indirectly by reducing the rate of diffusion of sodium into the cell. Thus, inhibition of sodium-potassium ATPase leads to an increase in intracellular sodium concentration and a reduced gradient for sodium entry. Second, phosphate transport can be modified directly and specifically in the presence of a constant sodium gradient by alteration of either the affinity of the brush-border membrane for phosphate or the V_{max} or capacity of the uptake system itself. Under most conditions, the capacity of the brush-border system seems to be the rate-limiting step in renal phosphate transport. Favoring this concept is the demonstration that most factors that alter net proximal reabsorption of phosphate in vivo similarly alter net phosphate uptake by brush-border membrane vesicles prepared from treated animals [2]. In addition, a decrease in sodium-dependent phosphate transport is observed in vesicles isolated from animals acutely given PTH and cyclic AMP [10] and in animals chronically given $1,25(OH)_2D_3$ [11]; increases in uptake have been observed repeatedly in vesicles prepared from animals treated with a low-phosphate diet [2].

The mechanism by which modifiers of phosphate transport alter brush-border uptake is an area of intense investigation. Although initial studies suggested a correlation with membrane-bound alkaline phosphatase activity, more recent studies have dissociated enzyme activity and phosphate transport [12]. Nicotinamide administration in vivo but not in vitro leads to phosphaturia, specific inhibition of sodium-dependent brush-border membrane phosphate uptake, and increased renal cortical NAD levels [13]. Because NAD added to vesicles also inhibits brush-border uptake, it has been suggested that cytoplasmic NAD levels, by interacting with membrane protein, could serve as a physiologic control of phosphate transport. Circumstantial evidence marshaled for this hypothesis includes the demonstration that phosphaturic factors such as PTH, cAMP, glucocorticoid administration, and metabolic acidosis stimulate gluconeogenesis, and thereby NAD levels [13]. Additionally or alternatively, cAMP may directly alter a membrane transport protein by protein kinase-mediated phosphorylation. In accord with this hypothesis, recent studies demonstrated cAMP-dependent phosphorylation of 2 protein bands (MW = 96,000 and 62,000) in brush-border membrane vesicles in vitro, and this phosphorylation was associated with a significant decrease in sodium-dependent phosphate, but not D-glucose, transport [14].

Relationship between phosphate transport and vitamin D metabolism. As stated, the effect of vitamin D on phosphate transport remains controversial. Although recent studies clearly demonstrate increased intestinal phosphate absorption with $1,25(OH)_2D_3$ administration [15], experimental data relating to effects on the kidney are variable and conflicting [16]. It has not been possible to demonstrate effects of D metabolites on phosphate transport in normal subjects when parathyroid hormone is controlled, but changes can be observed in selected conditions. Parenteral administration of $1,25(OH)_2D_3$ to animals receiving vasopressin or PTH, that is, animals with increased basal intrarenal cAMP levels, reduces phosphate excretion acutely [17, 18]. Also, $25(OH)D_3$ reduces urinary cAMP excretion [18]. In sharp contrast to these acute changes, chronic treatment of parathyroidectomized animals with $1,25(OH)_2D_3$ reduces the elevated Tm for phosphate and increases phosphate excretion [19]. Recent studies in isolated cells corroborate both of these seemingly discrepant observations [20]. Liang and coworkers found that administration of $1,25(OH)_2D_3$ to vitamin D-deficient chicks was associated with increased phosphate uptake by isolated renal tubular cells when studied 3 hours later; 17 hours later, however, phosphate uptake was reduced. In both these studies and those involving chronic administration of vitamin D to thyroparathyroidectomized animals, the serum phosphate level had increased by the time phosphaturia occurred in vivo or when decreased cellular uptake was observed in vitro. It is therefore possible that acute administration of $1,25(OH)_2D_3$ stimulates phosphate uptake, but that chronic administration represents a more complex situation in which changes in filtered load and cellular phosphate concentration produce different effects. The relationship of these observations to homeostatic regulation of phosphate and disordered states of phosphate homeostasis remains unclear, however. As I will discuss subsequently, the relationship between tubular phosphate transport and vitamin D metabolism in vitamin D-resistant rickets is an area of intense interest. In addition to the putative effects of vitamin D metabolites on phosphate transport, it is clear that phosphate is an important regulator of $25(OH)D_3$-1α hydroxylase activity. Thus in humans and experimental animals, phosphate deprivation is a potent stimulus to $1,25(OH)_2D_3$ production, as is parathyroid hormone [4, 21, 22]. Another intriguing relationship between phosphate transport and $1,25(OH)_2D_3$ is the localization of the site of $1,25(OH)_2D_3$ and $24,25(OH)_2D_3$ production to the proximal tubule, the major site of phosphate transport [23, 24].

Differential diagnosis of chronic hypophosphatemia

Hypophosphatemia can reflect a negative phosphate balance and body deficits of phosphate. It also can be produced acutely if the cellular uptake of phosphate is increased at the expense of the extracellular fluid concentration. The latter instance, which occurs with acute disturbances such as respiratory alkalosis and insulin administration, or with hyperalimentation, has been discussed previously in this forum by Eberhard Ritz [25]. Because phosphate is absorbed from the gastrointestinal tract

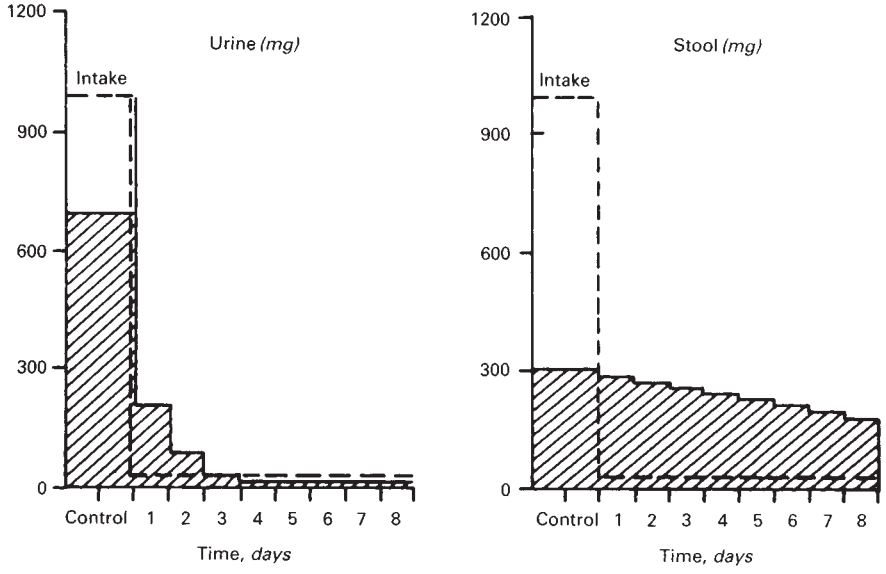

Fig. 2. *Urinary and fecal phosphate excretion in man in response to phosphate deprivation.* (Adapted from Ref. 2.)

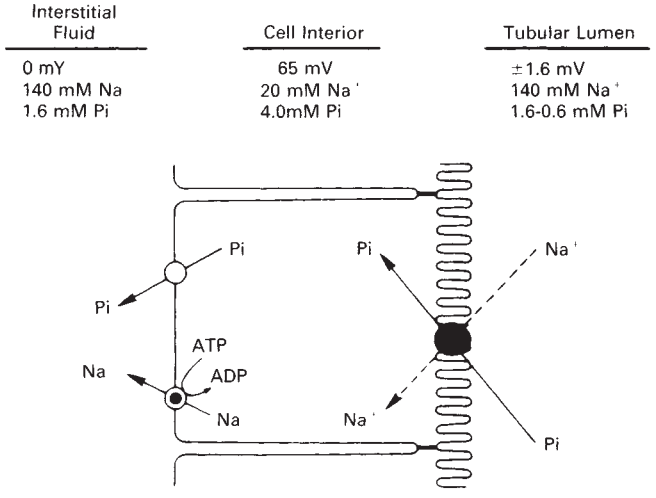

Fig. 3. *Conceptual model of phosphate transport in the proximal convoluted tubule.* The essential elements include Na-Pi cotransport at the brush border membrane and phosphate diffusion at the antiluminal membrane. The energy for phosphate entry is provided by the sodium concentration gradient. (From Ref. 2; © S. Karger AG, Basel.)

and undergoes renal excretion, negative phosphate balance reflects a disturbance in one or both of these organ systems. Under normal conditions, approximately 60% to 70% of dietary phosphorus is absorbed from the gastrointestinal tract, principally in the small bowel. At the same time, approximately 200 mg of phosphate per day is secreted into the stool. Gastrointestinal phosphate absorption can be increased by the administration of vitamin D metabolites, but there seems to be little modulation or control of gastrointestinal secretion. Thus, although the kidney adapts quickly to dietary phosphate deprivation, continued loss of phosphate into the stool over a prolonged period can produce negative phosphate balance and hypophosphatemia [4]. A more severe negative phosphate balance due to increased phosphate loss in the stool occurs with antacid administration because antacids bind phosphate in the intestinal lumen. Thus, clinical situations exist in which significant chronic hypophosphatemia can be a manifestation of gastrointestinal phosphate loss. This entity can be suspected from the patient's medical history and can be documented by an evaluation of the urinary phosphate excretion. As we have seen, the renal adaptation to decreased phosphate intake is characterized by virtual elimination of phosphate from the urine. The presence of significant amounts of phosphate in the urine, that is, more than 100 mg per 24 hours, in the presence of severe hypophosphatemia (less than 2 mg/dl) indicates that the kidney is not responding appropriately and further indicates that renal phosphate wasting is contributing, in part or in total, to the hypophosphatemia.

As I have already discussed, in addition to dietary phosphate intake, parathyroid hormone is the other important regulator of urinary phosphate excretion. Inappropriate urinary phosphate excretion therefore implies either increased secretion of parathyroid hormone or a defect in the normal tubular transport of phosphate (Table 2). Elevations of parathyroid hormone in turn reflect either a primary abnormality of parathyroid secretion (primary hyperparathyroidism) or increased secretion due to a disturbance in calcium homeostasis that lowers the serum calcium, such as intestinal malabsorption or disturbances in vitamin D metabolism. Urinary phosphate wasting in the absence of increased levels of PTH can be an isolated defect, can exist in association with idiopathic hypercalciuria, or can be part of a generalized defect in proximal tubular function (Fanconi syndrome) that is associated with varying combinations of glucosuria, aminoaciduria, uricosuria, and bicarbonate wasting. The isolated defect variably referred to as phosphate diabetes, familial hypophosphatemic rickets, or vitamin D-resistant rickets can be manifested as a familial X-linked syndrome or as an acquired form of vitamin D-refractory osteomalacia, which often is associated with mesenchymal tumors.

The patient under discussion today manifested renal phosphate wasting in the presence of normal parathyroid hormone levels. There was no evidence of a disturbance in renal tubular transport of glucose, amino acids, or uric acid, and she had no family history of bone disease. Removal of a vascular tumor was associated with immediate correction of the phosphate

Table 2. Renal phosphate wasting syndromes

Primary hyperparathyroidism
Vitamin D defiency with secondary hyperparathyroidism
Lack of calciferol
Diet
Malabsorption
Inadequate sunlight
Lack of 25-hydroxycholecalciferol
Liver disease
Phenobarbital, phenytoin
Nephrotic syndrome
Lack of $1,25(OH)_2D_3$
Vitamin D-dependent rickets
Phosphate transport defect
Isolated: Vitamin D-resistant rickets
Familial
Adult sporadic (with or without glycinuria)
Idiopathic hypercalciuria
Tumor associated (oncogenic osteomalacia)
Generalized: Fanconi syndrome

transport abnormality and she therefore represents an example of tumor-induced, or oncogenic, osteomalacia.

Pathogenesis of vitamin D-resistant rickets

Renal phosphate wasting and disordered bone formation characterize the familial disorder of X-linked hypophosphatemic rickets [26]. Because of the similarities between the clinical presentation of this disease and vitamin D deficiency, and because of the condition's resistance to physiologic replacement doses of vitamin D, the disorder also has been termed vitamin D-resistant rickets. Its cause has been difficult to define, and investigation has focused on two hypotheses. The first hypothesis posits a primary abnormality in vitamin D metabolism that results in decreased intestinal absorption of calcium and phosphate; secondary hyperparathyroidism in turn produces renal phosphate wasting, hypophosphatemia, and skeletal abnormalities. The second hypothesis postulates that the primary defect resides in the renal tubule itself and leads to deficient reabsorption of phosphate; hypophosphatemia is perceived as the cause of the skeletal abnormalities. Although most investigators agree that the kidney plays the primary role in the phosphate wasting, the exact nature of the defect and the role of vitamin D metabolites in the pathogenesis of the defect remain unclear. I would like to summarize some of the recent progress in this area, although unfortunately it is not yet possible to tie all of the new data together into a neat package.

Secondary hyperparathyroidism versus intrinsic renal tubular defect. Three lines of evidence argue against diminished gut calcium transport and consequent secondary hyperparathyroidism as the underlying cause of vitamin D-resistant rickets. Earlier studies, which had suggested that calcium infusion could decrease phosphate excretion in patients with this disease, implied that parathyroid hormone played a pathogenetic role [27]. It now is clear that PTH levels are normal in untreated patients [28–30] but that phosphate transport does respond to manipulation of PTH secretion. Second, treatment with large doses of vitamin D or its metabolites does not alter the phosphate transport defect despite a markedly positive calcium balance and normal levels of PTH [31]. Probably the most convincing data, however, have come from studies of an animal model. The Hyp Y mouse developed by Eicher and colleagues exhibits X-linked familial hypophosphatemia, renal phosphate wasting, and rickets, and is presumed to be a relevant animal model of the disease in humans [32]. Micropuncture studies demonstrated decreased proximal tubular phosphate reabsorption [33]. Most important, although phosphate reabsorption increased following parathyroidectomy, the rate of transport remained low compared to that in controls (Fig. 4). This transport rate was not increased to the levels observed in controls despite infusion of phosphate and an increase in filtered load (Fig. 5). Decreased phosphate uptake has been localized to the brush-border membrane in vesicle studies of membranes from affected mice [34].

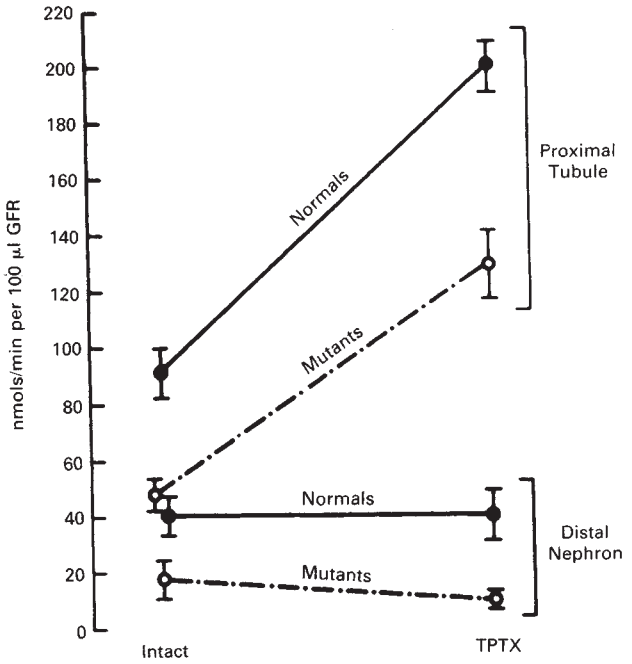

Fig. 4. *Phosphate transport rate in the proximal tubule and distal nephron in normal mice* (solid circles) *and hypophosphatemic littermates* (mutants, open circles) *before and after thyroparathyroidectomy* (TPTX). Note reduced transport rate in the intact mutant mice compared to controls. With TPTX, transport rate increases but remains reduced in mutants compared to controls. (Reproduced from *The Journal of Clinical Investigation*, 1979, 63:1203, by copyright permission of The American Society for Clinical Investigation [33].)

Defective vitamin D metabolism. Despite evidence that secondary hyperparathyroidism is not the proximate cause of the renal phosphate wasting in vitamin D-resistant rickets, evidence is emerging that a defect in vitamin D metabolism plays a role in some disease manifestations. Although levels of $1,25(OH)_2D_3$ are normal in affected humans [28] and mice [35], the normal levels are inappropriately low for the prevailing level of serum phosphate, because hypophosphatemia produced by phosphate depletion is normally a potent stimulus to $1,25(OH)_2D_3$ production. This phenomenon has been demonstrated in control mice in which phosphate restriction significantly increased $1,25(OH)_2D_3$ levels, whereas $1,25(OH)_2D_3$ decreased below normal in Hyp Y affected mice [35]. In a separate study, direct measurements of $25(OH)D_3$-1α hydroxylase activity in mouse kidney revealed that phosphate depletion of normal mice sufficient to achieve serum phosphate levels comparable to those in the affected mice resulted in a fourfold

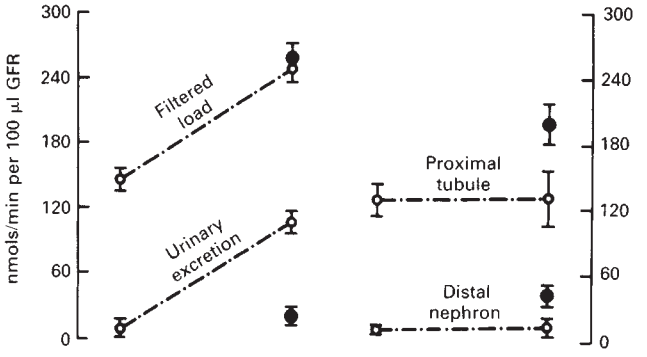

Fig. 5. *Effects of phosphate infusion on transport rate in nephron of TPTX hypophosphatemic mice.* Note that despite increase in filtered load to levels comparable to control TPTX mice (*solid circles*), the transport rate remains reduced in hypophosphatemic mutants (*open circles*) in proximal tubule and distal nephron. Thus, defective phosphate transport persists in the mice despite the absence of PTH. (Reproduced from *The Journal of Clinical Investigation*, 1979, 63:1203, by copyright permission of The American Society for Clinical Investigation [33].)

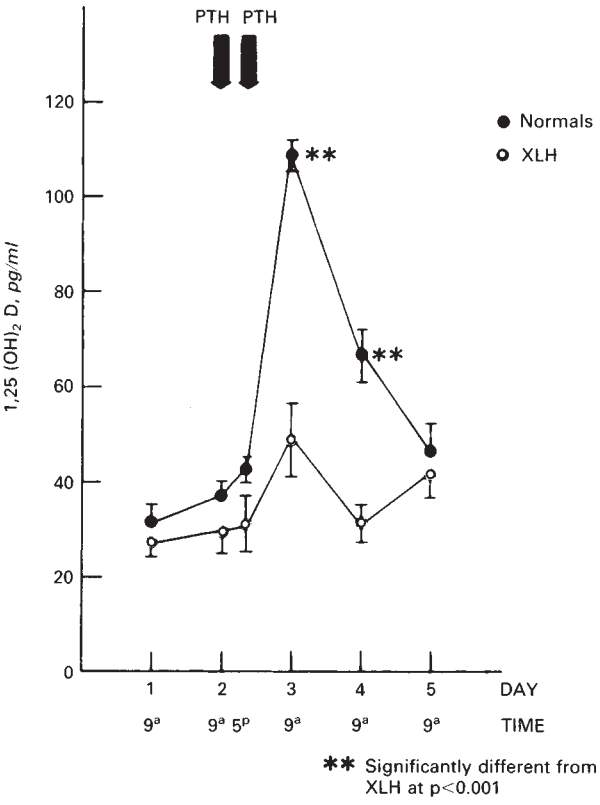

Fig. 6. *Effects of PTH on serum 1,25(OH)$_2$D$_3$ levels in normal subjects and patients with X-linked hypophosphatemia* (XLH). Note that the levels increased significantly in both groups but were significantly greater in normals than in patients. (Reproduced from Ref. 37.)

greater increase in 25(OH)D$_3$-1α hydroxylase activity than that in affected mice [36]. Finally, as illustrated in Figure 6, Lyles and Drezner showed that intravenous administration of PTH, a potent stimulator of 25(OH)D$_3$-1α hydroxylase activity in normal humans, produced a much smaller increment in 1,25(OH)$_2$D$_3$ concentration in patients with X-linked hypophosphatemic rickets despite equivalent increases in urinary cAMP excretion [37].

Sporadic, adult-onset vitamin D-resistant rickets and tumor-induced osteomalacia. Sporadic, nonfamilial, vitamin D-resistant rickets first appearing in adulthood was initially described by McCance in 1947 [38]. Over the next 25 years, approximately 20 patients were characterized by Dent and Stamp [39]. Clinical features included bone pain, muscle weakness, and loss of height due to vertebral collapse. Radiologically and biochemically, these patients' disease appeared identical to the sex-linked form, with the additional feature in some of increased urinary glycine excretion. In 1970, Salassa, Jowsey, and Arnaud called attention to the syndrome of recovery from adult-onset hypophosphatemic osteomalacia after removal of benign soft-tissue tumors [40]. The authors reported 2 patients and reviewed 4 others from the literature. It is interesting that one of those 4 was McCance's original patient who completely recovered from phosphate wasting coincident with the removal of a tumor of the femur [41]. Since 1970 approximately 40 more patients with tumor-induced osteomalacia have been reported [42–48]. In many of these, the tumors were found because they were close to the surface, large, or because they invaded skeletal structures. One can speculate that small, clinically inapparent tumors hidden in extraskeletal connective tissue may go undetected in some patients currently thought to have sporadic vitamin D-resistant rickets. The patient discussed today, for example, underwent extensive evaluation for a tumor when she was originally hospitalized, but none was found. Because many of these lesions are vascular, there is considerable promise that blood-pool scans will prove a sensitive tool for detecting clinically silent tumors.

In addition to the defect in phosphate excretion, these patients usually manifest low plasma levels of 1,25(OH)$_2$D$_3$ despite decreases in serum phosphate and normal levels of 25(OH)D$_3$ and PTH [43–45]. I should emphasize that decreased levels of 1,25(OH)$_2$D$_3$ in these patients, in contrast to the "inappropriately" normal levels in the patients with familial disease, might serve as a marker for the presence of a tumor. Although most of the patients in the original reports had neoplasms of mesenchymal origin, often giant cell vascular tumors, the syndrome recently was described in patients with prostate carcinoma, with breast carcinoma, and with the epidermal nevus syndrome [44–46]. Remission of the syndrome with removal of the tumor obviously suggests a humoral origin, but direct demonstration of this pathogenetic mechanism is lacking. Three studies have suggested evidence of phosphaturic activity in saline extracts of such tumors [46–48]. More recently, Lyles et al transplanted tumor tissue from an affected patient with prostatic cancer into athymic nude mice [49]. The tumor-bearing mice developed phosphate wasting, hypophosphatemia, and defective 25(OH)D$_3$-1α hydroxylase activity.

Relationship between abnormal phosphate transport and abnormal vitamin D metabolism. The concurrence of similar metabolic defects in phosphate transport and vitamin D metabolism in X-linked hypophosphatemic rickets in humans and in the mouse model, as well as in tumor-induced osteomalacia in humans, clearly suggests a relationship between these defects. Although not as well characterized, paradoxically normal levels of 1,25(OH)$_2$D$_3$ in the presence of hypophosphatemia also have been observed in the Fanconi syndrome [50]. Further, the similarity between sites of tubular phosphate transport and sites

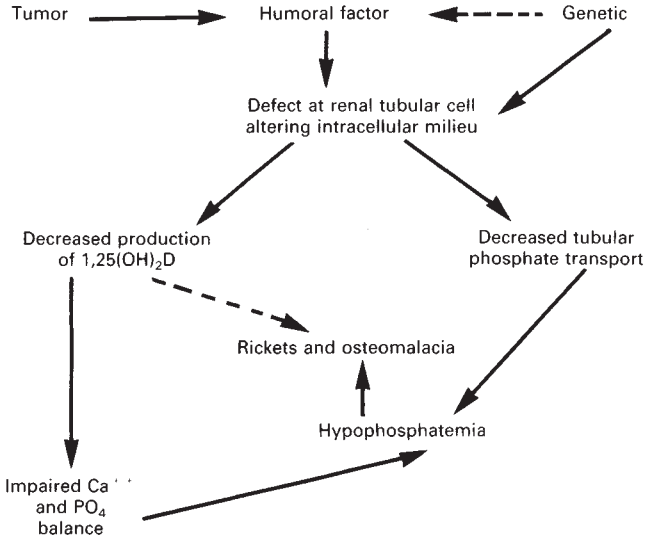

Fig. 7. *Model of the pathophysiology of vitamin D-resistant rickets.* Components of the model are speculative (see text).

of $1,25(OH)_2D_3$ production suggests that a single cellular defect might explain the abnormalities in phosphate transport and in vitamin D metabolism. A simple defect reducing phosphate traffic through the cell cannot adequately explain these observations, because increased levels of $1,25(OH)_2D_3$ are found in patients with phosphate depletion, parathyroid hormone excess, and idiopathic hypercalciuria with phosphate wasting [51]. On the other hand, diminished $1,25(OH)_2D_3$ production cannot explain the phosphate transport defect, because $1,25(OH)_2D_3$ levels are not low in the familial forms despite the presence of the defect; physiologic replacement doses of vitamin D or its metabolites do not correct the transport defect [52], and the effects of chronic administration of $1,25(OH)_2D_3$ on phosphate transport are, if anything, inhibitory rather than stimulatory [19]. We currently can only speculate that an alteration in the intracellular milieu is responsible for defective $1,25(OH)_2D_3$ production and phosphate transport (Fig. 7). The fact that patients with tumor-induced osteomalacia manifest identical abnormalities, both of which are transferable by transplanting tumor tissue, raises the possibility of an unidentified humoral agent. Again, one can speculate that X-linked hypophosphatemic rickets is a genetically transmitted endocrinopathy associated with autonomous production of this unknown factor, but none of the studies to date in patients or hypophosphatemic mice have adequately addressed this possibility. Culture of proximal tubule cells from affected mice and of the cells' transport characteristics should provide important new information in this regard.

Therapeutic approach

While we remain ignorant of the cellular abnormality responsible for the transport defect, we can reasonably state that the attendant signs and symptoms are the consequence of disordered mineral metabolism. Phosphate depletion both in humans and in experimental animals causes osteomalacia despite increased levels of $1,25(OH)_2D_3$. One initially might suppose that treatment should consist of administration of large doses of phosphate. But phosphate administration reduces intestinal calcium absorption, lowers serum calcium, and produces secondary hyperparathyroidism. Increased levels of parathyroid hormone can aggravate the bone disease both directly and indirectly by decreasing renal phosphate reabsorption. Given that $1,25(OH)_2D_3$ levels are inappropriately low, and that vitamin D deficiency produces similar bone lesions, these patients can reasonably be treated with vitamin D. Although this therapeutic regimen can raise serum phosphate somewhat, it is not curative. The increase in serum phosphate following vitamin D therapy probably reflects a combination of increased gastrointestinal absorption as well as suppression of PTH levels and allows increased tubular transport of phosphate. Because these patients might not be able to adequately convert $25(OH)D_3$ to $1,25(OH)_2D_3$, therapeutic levels of $1,25(OH)_2D_3$ may not be achieved despite large doses of vitamin D_2 [31]. A therapeutic regimen therefore must be designed with the following goals in mind: to increase serum phosphate (by increasing gastrointestinal absorption), prevent secondary hyperparathyroidism, suppress PTH if possible, and provide levels of $1,25(OH)_2D_3$ sufficient to promote bone healing. The ideal therapy probably comprises a combination of $1,25(OH)_2D_3$, calcium, and phosphate. Lyles, Harrelson, and Drezner showed that although large doses of vitamin D_2 in combination with oral phosphate and calcium improved phosphate balance and increased serum phosphate and $25(OH)D_3$ levels, this regimen actually suppressed $1,25(OH)_2D_3$ levels and did not completely heal the bone lesions [31]. Similarly, physiologic doses of $1,25(OH)_2D_3$ produce some improvement in phosphate balance but do not heal the bone disease [53]. High-dose therapy sufficient to produce marked increases in serum $1,25(OH)_2D_3$ does seem to completely heal the bone abnormalities. A combination of 3 μg/day of $1,25(OH)_2D_3$ and 2 g/day of oral phosphorus completely healed the histologic abnormalities [54]. With this regimen, serum phosphate and TmP/GFR both increased to the normal range. Plasma levels of $1,25(OH)_2D_3$ increase markedly above normal with this regimen and, although the serum calcium level remains normal, urinary calcium excretion increases markedly; presumably this rise reflects suppression of parathyroid hormone. For complete healing of bone disease, normal levels of serum phosphate probably are necessary (Fig. 8). Achieving normal levels of serum phosphate in the presence of a renal transport defect requires a marked increase in intestinal phosphate absorption in combination with suppression of PTH secretion. Patients with vitamin D-resistant rickets, in addition to having the renal transport defect, do not respond normally to negative phosphate balance with increased $1,25(OH)_2D_3$ production. The therapeutic regimen therefore must include phosphate and large doses of $1,25(OH)_2D_3$. Whether the increased levels of $1,25(OH)_2D_3$ play a direct role in improving mineralization in addition to increasing serum phosphate cannot be determined from the available data and remains to be investigated.

Questions and answers

DR. NICOLAOS E. MADIAS: You have indicated that removal of the tumor in patients with tumor-associated vitamin D-resistant rickets leads to remission of the syndrome, suggesting the presence of a tumor-generated, humoral, phosphaturic principle. You also have speculated that the autonomous production of such a factor might be responsible for the metabolic

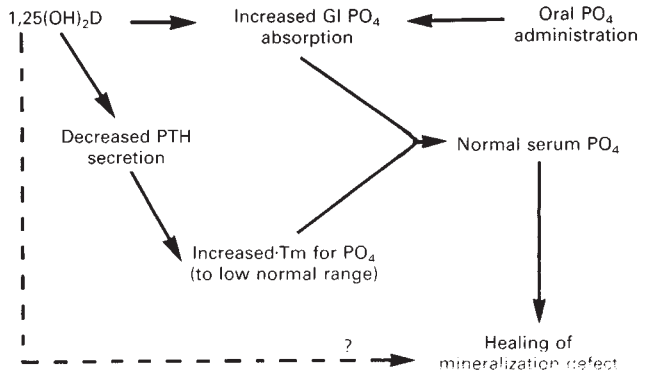

Fig. 8. *Therapeutic approach to vitamin D-resistant rickets.*

defects observed in X-linked hypophosphatemic rickets in humans and in the mouse model. This hypothesis implies that nothing is inherently wrong with the renal tubule itself. Has this thesis ever been tested in the mouse model using either microperfusion or transplantation?

DR. AGUS: No, not directly. No studies have utilized in-vitro perfusion of tubules dissected from the mice and, to my knowledge, no one has attempted cross-circulation or transplantation experiments. As the defect is apparent in brush-border membrane vesicles isolated from the kidneys of affected mice, one could suggest that this is evidence of an intrinsic defect. Vesicles from animals with acquired metabolic or hormonal disturbances of phosphate transport (such as phosphate depletion or parathyroidectomy) also exhibit alterations in vitro, however. The argument is therefore not convincing.

DR. JOHN T. HARRINGTON: The phosphate wasting in this patient with tumor-induced phosphaturia disappeared within 48 hours of removal of the tumor. Assuming that this phenomenon is due to a humoral factor, one would anticipate that the 1,25-dihydroxy-vitamin D levels also would return to normal within 48 hours. Has anyone measured 1,25-dihydroxy-vitamin D levels 1 or 2 days after operation in such patients to determine whether this hypothesis is correct?

DR. AGUS: Yes, Sweet and coworkers demonstrated a progressive rise in $1,25(OH)_2D_3$ beginning as soon as 24 hours after removal of a hemangioma in a patient with oncogenic osteomalacia [45].

DR. JEROME P. KASSIRER: What is known at a molecular level about the factor that instigates the phosphaturia?

DR. AGUS: At present we have no direct information of this type; the evidence for the existence of this factor is circumstantial. Three groups have been able to demonstrate phosphaturia with saline extracts of the tumor [46–48], and phosphaturia is transferable with tumor transplantation [49]. Isolation, identification, and characterization of the phosphaturic principle have not been accomplished.

DR. KASSIRER: In comparing vitamin D-resistant rickets of the familial variety and the variety secondary to tumors, does one find any distinguishing characteristics other than the disappearance of the syndrome when the inciting tumor is removed?

DR. AGUS: In the familial syndrome, $1,25(OH)_2D_3$ levels are within the normal range, albeit inappropriate for the degree of hypophosphatemia. In patients with the tumor-associated syndrome, these levels are truly low. The $1,25(OH)_2D_3$ level therefore is a very important marker for the presence of a tumor, at least at the moment; anyone who presents with sporadic vitamin D-resistant rickets and a low $1,25(OH)_2D_3$ level should be presumed to have a tumor until proven otherwise. As recognition of this marker has taken place only within the last several years, it would be important to check levels in these patients who are currently being followed.

DR. HARRINGTON: Do these patients given high doses of 1,25-dihydroxy-vitamin D—amounts three to four times a physiologic dose—become hypercalcemic?

DR. AGUS: Long-term experience with this regimen is very limited. Dr. Marc Drezner, who has treated several patients in this fashion, suggests that hypercalcemia does not become a problem until the bone lesions are healed. Supraphysiologic doses of $1,25(OH)_2D_3$ can be necessary for as long as a year to heal bone lesions, and the dosage may have to be decreased thereafter.

DR. DAVID CAHAN (*Chief of Nephrology, Faulkner Hospital, Boston*): Do all patients who meet the chemical criteria for having renal phosphate wasting with a low 1,25-vitamin D level develop rickets? I ask because my practice contains a family that I have been puzzled over for a few years. The father is 80 years old; the two sons are about 60 years old. Phosphate wasting, inappropriately low to normal $1,25(OH)_2D_3$ levels, and normal PTH levels are present, but no evidence of tumor or radiologic evidence of bone disease has been found so far in any of the 3 patients.

DR. AGUS: Patients with a familial syndrome characterized by reduced tubular reabsorption of phosphate, hypophosphatemia, and normal levels of PTH without rickets have been described. These people often have bone alterations, but the lesions usually are much less severe than are those in the typical patient with vitamin D-resistant rickets [55]. We have insufficient information at present to know whether differences exist in vitamin D metabolism in these patients, or whether they represent a milder form of the disease.

DR. JERRY MCCAULEY (*Division of Nephrology, NEMC*): Is there any evidence that this humoral substance is a prostaglandin?

DR. AGUS: We have no direct evidence, but administration of aspirin or indomethacin has no effect on the expression of the disease. In normal individuals, these drugs also have little effect on phosphate transport.

DR. ANDREW LEVEY (*Division of Nephrology, NEMC*): You mentioned earlier that phosphorus-depleted animals have increased fractional tubular reabsorption of phosphate not attributable to parathyroid hormone or vitamin D. Have experiments been performed to examine whether this effect is the result of alterations in a different humoral substance? For instance, it is interesting to speculate that under normal circumstances baseline levels of such a hormone might contribute to phosphate reabsorption, phosphate depletion might reduce hormone levels and lead to renal phosphate conservation, and ectopic production by a tumor might result in phosphate wasting.

DR. AGUS: The hypothesis is certainly an interesting one but to date has not proven fruitful. Attempts by Bonjour et al to transmit the adaptive response in rats with plasma or whole blood from phosphate-depleted animals have not been successful [56]. In addition, Brazy and coworkers were unable to demonstrate effects of plasma on phosphate transport in isolated perfused proximal tubules from phosphate-depleted animals,

whereas perfused tubules from phosphate-depleted animals exhibited increased transport despite perfusion for more than an hour with fluids derived from normal animals [57].

DR. LEVEY: Does this syndrome produce alterations in other vitamin D metabolites, such as 24,25-dihydroxy-vitamin D_3?

DR. AGUS: I am not aware of direct measurements of 24,25-dihydroxy-vitamin D_3 in patients with familial vitamin D-resistant rickets. Many factors including phosphate seem to influence 1-alpha hydroxylation and 24-hydroxylation of $25(OH)D_3$ in a reciprocal fashion. I would not be surprised therefore to find elevated levels of $24,25(OH)_2D_3$ in this syndrome. In one patient with oncogenic osteomalacia, $24,25(OH)_2D_3$ levels were found to be normal at the same time that low levels of $1,25(OH)_2D_3$ were documented [45].

DR. KASSIRER: Coe asserts that the primary disorder in idiopathic hypercalciuria is a primary renal calcium leak [63, 64]. You listed idiopathic hypercalciuria as a disorder of phosphate transport. What is the evidence for disordered phosphate metabolism, and do you have a hypothesis that links it to hypercalciuria?

DR. AGUS: In an early description of the syndrome of idiopathic hypercalciuria, Albright and colleagues pointed out the association with hypophosphatemia [58]. The issue has been controversial since that time, and frank hypophosphatemia (serum phosphate less than 2.5 mg/dl) generally is considered to be distinctly unusual. On the other hand, the mean serum phosphate in these patients usually is lower than the mean value in a group of normocalciuric patients [51, 59, 60]. In addition, when urine phosphate is factored for serum phosphate and filtered load of phosphate ($TmPO_4$/GFR), most investigators find reduced reabsorption, evidence for a tubular defect in phosphate transport. In addition to a defect in tubular phosphate transport, which persists after reduction of PTH with calcium infusion [51], we and others have found evidence for a defect in proximal tubule sodium transport in these patients [51, 61]. Increased levels of $1,25(OH)_2D_3$ also have been described, and most investigators concur that PTH levels are rarely increased in patients with idiopathic hypercalciuria [51, 61–63]. The original suggestion of a primary renal calcium leak causing negative calcium balance and secondary hyperparathyroidism thus no longer seems tenable. Experimental phosphate depletion produces increased levels of $1,25(OH)_2D_3$, increased gut calcium absorption, increased bone resorption, and a defect in renal tubular calcium transport [1]. We and others have suggested that these tubular abnormalities and alterations in phosphate metabolism could produce the hypercalciuria in these patients. This could occur in several ways. Increases in levels of $1,25(OH)_2D_3$ due to either altered proximal tubular function or hypophosphatemia could lead to increased gut absorption and bone resorption. This change would be expressed clinically as either diet-dependent calciuria, fasting calciuria on a low-calcium diet, or both. Each of these situations would present as hypercalciuria without elevated levels of PTH. In fact, most patients with idiopathic hypercalciuria probably exhibit elements of both hyperabsorption and fasting calciuria with negative calcium balance on a low-calcium diet. In addition, the unusual patient with calciuria and elevated PTH levels would be explained by renal calcium loss due to either a primary tubular defect or direct effects of hypophosphatemia on renal tubular calcium transport.

DR. KASSIRER: I believe Coe acknowledges that the PTH levels are normal, but he still believes that the renal leak is primary in almost all cases.

DR. AGUS: I think the issue is partly a semantic one. As originally defined, diagnosis of a renal leak required the presence of elevated levels of PTH [64]. The definition currently is being broadened so that it no longer requires increased PTH but includes patients with negative calcium balance, that is, those with urinary calcium excretion that exceeds calcium intake [63]. This situation could occur with increased bone resorption as well as with a primary renal calcium leak. The increased excretion could be due to suppressed PTH, effects of phosphate depletion on calcium transport, increased levels of $1,25(OH)_2D_3$, or a defect in transport of sodium, calcium, or both. I think both Dr. Coe and I agree that the separation of patients with idiopathic hypercalciuria into renal and absorptive subgroups is no longer useful [63] and that definition of the role and mechanism of disordered phosphate metabolism and elevated levels of $1,25(OH)_2D_3$ deserves careful attention.

DR. MADIAS: Do micropuncture studies demonstrate a defect in proximal tubular sodium reabsorption, in addition to decreased phosphate reabsorption, in the mouse model of vitamin D-resistant rickets?

DR. AGUS: In the 2 reported studies, no defect in sodium transport was identified. But it is possible that a subtle defect escaped detection.

DR. HARRINGTON: In normal individuals who are phosphate restricted and in whom urinary phosphate excretion is essentially zero, what kinds of stimuli increase the urinary phosphate excretion? I am interested in knowing the relative strength of the factors that regulate renal tubular phosphate reabsorption.

DR AGUS: Several factors have been shown to increase phosphate excretion and restore responsiveness to PTH in phosphate-depleted animals. These include ammonium chloride-induced acidosis [65, 66], administration of nicotinamide [13], and chronic administration of $1,25(OH)_2D_3$ in TPTX rats [19]. In addition, recent studies have shown that glucocorticoids and glucagon also can increase phosphate excretion in phosphate-depleted animals [67, 68]. Whether these various factors act independently or through a common pathway such as gluconeogenesis is obviously receiving intense interest.

DR. MICHAEL MADAIO (*Division of Nephrology, NEMC*): I noticed that you posit phenytoin-induced osteomalacia as a defect in 25-hydroxy-vitamin D. As you know, it has been shown that $1,25(OH)_2D_3$ levels are normal in these patients [69]. Is this another cause of vitamin D-resistant rickets? If so, could this agent be a probe to the study of the mechanism of the defect induced?

DR. AGUS: Despite reductions in $25(OH)D_3$, $1,25(OH)_2D_3$ levels are not low in anticonvulsant-induced osteomalacia [69]. In another series, 1,25-dihydroxy-vitamin D_3 levels are not low despite reductions in $24,25(OH)_2D_3$ [70]. Anticonvulsants can directly inhibit vitamin D-stimulated active intestinal calcium transport [71], and they also can impair both PTH-mediated and non-PTH-mediated bone resorption [72]. The mechanism of the hypocalcemia and osteomalacia therefore is probably multifactorial. But anticonvulsant-induced abnormalities are, for the most part, reversed by modest although pharmacologic doses of vitamin D [73]; in that sense this entity differs significantly from vitamin D-resistant rickets.

DR. MADIAS: Has calcitonin been implicated in the pathogenesis of this syndrome?

DR. AGUS: Calcitonin levels in this patient and in others with oncogenic osteomalacia have been normal [74]. Brunette and colleagues reported marked increases in calcitonin-sensitive adenylate cyclase activity in nephron segments of hypophosphatemic mice [75]. The physiologic significance of this observation has not been explained, however.

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References

1. AGUS ZS, GOLDFARB S, WASSERSTEIN A: Mineral metabolism in health and disease, in *Contemporary Nephrology*, edited by KLAHR S, MASSRY SG, New York, Plenum, 1981, vol. 1
2. DOUSA TP, KEMPSON SA: Regulation of renal brush border membrane transport of phosphate. *Miner Electrolyte Metab* 7:113–121, 1982
3. AGUS ZS: Renal handling of phosphate, in *Textbook of Nephrology*, edited by MASSRY S, GLASSOCK R, Baltimore, Williams and Wilkins, 1983
4. DOMINGUEZ JH, GRAY RW, LEMANN J JR: Dietary phosphate deprivation in women and men: Effects on mineral and acid balances, parathyroid hormone and the metabolism of 25-OH vitamin D. *J Clin Endocrinol Metab* 43:1056–1068, 1976
5. KREUSSER WJ, KUROKAWA K, AZNAR E, MASSRY SG: Phosphate depletion: Effect on renal inorganic phosphorus and adenine nucleotides, urinary phosphate and calcium, and calcium balances. *Miner Electrolyte Metab* 1:30–42, 1978
6. BONJOUR JP, TROEHLER U, PRESTON C, FLEISCH H: Parathyroid hormone and renal handling of phosphate: Effect of dietary phosphate and diphosphates. *Am J Physiol* 234:F497-F505, 1978
7. TROEHLER U, BONJOUR JP, FLEISCH H: Inorganic phosphate homeostasis: Renal adaptation to the dietary intake in intact and thyroparathyroidectomized rats. *J Clin Invest* 57:264–273, 1976
8. CHENG L, SACKTOR B: Sodium gradient-dependent phosphate transport in renal brush border membrane. *J Biol Chem* 256:1556–1564, 1981
9. HOFFMAN N, THEES M, KINNE R: Phosphate transport by isolated renal brush border vesicles. *Pfluegers Arch* 362:147–156, 1976
10. EVERS H, MURER H, KINNE R: Effect of parathyrin on the transport properties of isolated renal brush border vesicles. *Biochem J* 172:49–56, 1978
11. STOLL R, KINNE R, MURER H, FLEISCH H, BONJOUR JP: Phosphate transport by rat renal brush border membrane vesicles: Influences of dietary phosphate, thyroparathyroidectomy and 1,25-dihydroxy vitamin D. *Pfluegers Arch* 380:47–52, 1979
12. TENENHOUSE HS, SCRIVER CR, VIZEL EJ: Alkaline phosphatase activity does not mediate phosphate transport in the renal-cortical brush border membrane. *Biochem J* 190:473–476, 1980
13. KEMPSON SA, COLSON-OTERO G, LISE OU S-Y, TURNER ST, DOUSA TP: Possible role of nicotinamide adenine dinucleotide as an intracellular regulator of renal transport of phosphate in the rat. *J Clin Invest* 67:1347–1360, 1981
14. HAMMERMAN MR, HRUSKA KA: Cyclic AMP dependent protein phosphorylation in canine renal brush border membrane vesicles is associated with decreased phosphate transport. *J Biol Chem* 257:992–999, 1982
15. AVIOLI R, MILLER RA, BIRGE SJ: Characterization of phosphate uptake in isolated chick intestinal cells. *Adv Exp Med Biol* 128:399–404, 1980
16. LEVINE BS, BRAUTBAR N, COBURN JW: Does vitamin D affect the renal handling of calcium and phosphate? *Miner Electrolyte Metab* 1:295–302, 1978
17. PUSCHETT JB: Renal tubular effects of vitamin D and its metabolites. *Adv Exp Med Biol* 81:29–40, 1977
18. POPOVTZER MM, MEHANDRU S, SAGHAFI D, BLUM MS: Interactions between PTH, vitamin D metabolites and other factors in tubular reabsorption of phosphate. *Adv Exp Med Biol* 103:11–19, 1978
19. BONJOUR JP, PRESTON C, FLEISCH H: Effect of 1,25-dihydroxy vitamin D_3 on the renal handling of Pi in parathyroidectomized rats. *J Clin Invest* 60:1419–1428, 1977
20. LIANG CT, BARNES J, CHENG L, BALAKIR R, SACKTOR B: Effects of $1,25(OH)_2D_3$ administered in vivo on phosphate uptake by isolated chick renal cells. *Am J Physiol* 6:312–318, 1982
21. RADER JI, BAYLINK DJ, HUGHES MR, SAFILIAN EF, HAUSSLER MR: Calcium and phosphate deficiency in rats: Effects on PTH and 1,25-dihydroxy vitamin D_3. *Am J Physiol* 236:E118-E122, 1979
22. EISMAN JA, WARK JD, PRINCE RL, MOSELEY JM: Modulation of plasma 1,25-dihydroxy vitamin D in man by stimulation and suppression tests. *Lancet* 2:931–933, 1979
23. BRUNETTE MG, CHAN M, FERRIERE C, ROBERTS KD: Site of $1,25(OH)D_2$ vitamin D_3 synthesis in the kidney. *Nature* 276:287–289, 1978
24. KAWASHIMA H, TORIKAI S, KUROKAWA K: Localization of 25 hydroxy vitamin D_3 1α-hydroxylase and 24-hydroxylase along the rat nephron. *Proc Natl Acad Sci USA* 78:1199–1203, 1981
25. RITZ E: Nephrology Forum: Acute hypophosphatemia. *Kidney Int* 22:84–94, 1982
26. ALBRIGHT F, BUTLER AM, BLOOMBERG E: Rickets resistant to vitamin D therapy. *Am J Dis Child* 54:529–536, 1937
27. FALLS WF JR, CARTER N, RECTOR FW, SELDIN DW: Familial vitamin D resistant rickets: Study of six cases with evaluation of the pathogenic role of secondary hyperparathyroidism. *Ann Intern Med* 68:553–560, 1968
28. LYLES KW, CLARK AG, DREZNER MK: Serum 1,25-dihydroxy vitamin D levels in subjects with X-linked hypophosphatemic rickets and osteomalacia. *Calcif Tissue Int* 34:125–130, 1982
29. CHESNEY RW, MAZESS RB, ROSE P, HAMSTRA AJ, DELUCA HF: Supranormal 24-hydroxylase vitamin D and subnormal 1,25-dihydroxy vitamin D: their role in X-linked hypophosphatemic rickets. *Am J Dis Child* 134:140–143, 1980
30. SCRIVER CR, READE TM, DELUCA HF, HAMSTRA AJ: Serum 1,25-dihydroxy vitamin D levels in normal subjects and in patients with hereditary rickets or bone disease. *N Engl J Med* 299:976–979, 1982
31. LYLES KW, HARRELSON JM, DREZNER MK: The efficacy of vitamin D_2 and oral phosphate therapy in X-linked hypophosphatemic rickets and osteomalacia. *J Clin Endocrinol Metab* 54:307–315, 1982
32. EICHER EM, SOUTHARD JL, SCRIVER CR, GLORIEUX FH: Mouse model for human familial hypophosphatemic (vitamin D resistant) rickets. *Proc Natl Acad Sci USA* 73:4667–4671, 1976
33. COWGILL LD, GOLDFARB S, LAU K, SLATOPOLSKY E, AGUS ZS: Evidence for an intrinsic renal tubular defect in mice with genetic hypophosphatemic rickets. *J Clin Invest* 63:1203–1210, 1979
34. TENENHOUSE HS, SCRIVER CR, MCINNES RR, GLORIEUX FH: Renal handling of phosphate in vivo and in vitro by the X-linked hypophosphatemic male mouse: Evidence for a defect in the brush border membrane. *Kidney Int* 14:230–244, 1978
35. MEYER RA, GRAY RW, MEYER MH: Abnormal vitamin D metabolism in the X-linked hypophosphatemic mouse. *Endocrinology* 107:1577–1581, 1980
36. LOBAUGH B, DREZNER MK: Abnormal regulation of renal 25-hydroxy vitamin D-1-α-hydroxylase activity in the X-linked hypophosphatemic mouse. *J Clin Invest* 71:400–403, 1983
37. LYLES KW, DREZNER MK: Parathyroid hormone effects on serum 1,25-dihydroxy vitamin D levels in patients with X-linked hypophosphatemic rickets: Evidence for abnormal 25-hydroxy vitamin D-1α-hydroxylase activity. *J Clin Endocrinol Metab* 54:638–644, 1982
38. MCCANCE RA: Osteomalacia with Looser's nodes (milkman's syndrome) due to a raised resistance to vitamin D acquired about the age of 15 years. *Q J Med* 16:33–46, 1947
39. DENT CE, STAMP TCB: Hypophosphatemic osteomalacia presenting in adults. *Q J Med* 40:303–329, 1971
40. SALASSA RM, JOWSEY J, ARNAUD CD: Hypophosphatemic osteomalacia associated with "nonendocrine" tumors. *N Engl J Med* 283:65–70, 1970

41. DENT CE, FRIEDMAN M: Hypophosphatemic osteomalacia with complete recovery. *Br Med J* 1:1676–1679, 1964
42. EVANS DJ, AZZOPARDI JG: Distinctive tumors of bone and soft tissue causing acquired vitamin D-resistant osteomalacia. *Lancet* 1:353–354, 1972
43. DREZNER MK, FEINGLOS MN: Osteomalacia due to 1α,25-dihydroxy cholecalciferol deficiency: Association with a giant cell tumor of bone. *J Clin Invest* 60:1046–1053, 1977
44. LYLES KW, BERRY WR, HAUSSLER M, HARRELSON JM, DREZNER MK: Hypophosphatemic osteomalacia: Association with prostatic carcinoma. *Ann Intern Med* 93:275–278, 1980
45. SWEET RA, MALES JL, HAMSTRA AJ, DELUCA HF: Vitamin D metabolite levels in oncogenic osteomalacia. *Ann Intern Med* 93:279–280, 1980
46. ASCHINBERG LC, SOLOMON LM, ZEIS PM, JUSTICE P, ROSENTHAL IM: Vitamin D resistant rickets associated with epidermal nevus syndrome: Demonstration of a phosphaturic substance in the dermal lesions. *J Pediatr* 91:56–60, 1977
47. POPOVTZER MM: Tumor-induced hypophosphatemic osteomalacia: Evidence for a phosphaturic cyclic AMP-independent action of tumor extract. *Clin Res* 21:418A, 1981
48. LAU K, STOM MC, GOLDBERG M, GOLDFARB S, GRAY RW, LEMANN J JR, AGUS ZS: Evidence for a humoral phosphaturic factor in oncogenic hypophosphatemic osteomalacia. *Clin Res* 27:421A, 1979
49. LYLES KW, LOBAUGH B, PAULSON DF, DREZNER MK: Heterotransplantation of prostatic cancer from an affected patient creates an animal model for tumor-induced osteomalacia in the athymic nude mouse. *Calcif Tiss Int* 34:5–33, 1982
50. BREWER ED, TSAI HC, MORRIS RC: Evidence for impairment of metabolism of 25-hydroxy vitamin D_3 in children with Fanconi syndrome. *Clin Res* 24:154A, 1976
51. LAU Y-K, WASSERSTEIN A, WESTBY GR, BOSANAC P, GRABIE M, MITNICK P, SLATOPOLSKY E, GOLDFARB S, AGUS ZS: Proximal tubular defects in idiopathic hypercalciuria: Resistance to phosphate administration. *Miner Electrolyte Metab* 7:237–249, 1982
52. BRICKMAN AJ, COBURN JW, KUROKAWA K, BETHUNE JE, HARRISON H, NORMAN AW: Action of 1,25 dihydroxy cholecalciferol in patients with hypophosphatemic vitamin D-resistant rickets. *N Engl J Med* 289:495–498, 1973
53. RUSSELL RCG, SMITH R, PRESTON C, WALTON RJ, WOODS CG, HENDERSON RG, NORMAN AW: The effect of 1,25-dihydroxy cholecalciferol on renal tubular reabsorption of phosphate, intestinal absorption of calcium, and bone histology in hypophosphatemic renal tubular rickets. *Clin Sci Mol Med* 48:177–186, 1975
54. DREZNER MK, LYLES KW, HAUSSLER MR, HAZELTON JM: Evaluation of a role for 1,25-dihydroxy vitamin D_3 in the pathogenesis and treatment of X-linked hypophosphatemic rickets and osteomalacia. *J Clin Invest* 66:1020–1032, 1980
55. SCRIVER CR, MACDONALD W, READE T, GLORIEUX FH, NORGRADY B: Hypophosphatemic nonrachitic bone disease: An entity distinct from X-linked hypophosphatemia in the renal defect, bone involvement and inheritance. *Am J Med Genet* 1:101–117, 1977
56. BONJOUR JP, CAVERZASIO J, FLEISCH H, MUHLBAUER R, TROEHLER U: The adaptive system of the tubular transport of phosphate. *Adv Exp Med Biol* 151:1–12, 1982
57. BRAZY PC, MCKEOWN JW, HARRIS RH, DENNIS VW: Comparative effects of dietary phosphate, unilateral nephrectomy and parathyroid hormone on phosphate transport by the rabbit proximal tubule. *Kidney Int* 17:788–800, 1980
58. ALBRIGHT FP, HENNEMAN P, BENEDICT P, FORBES AP: Idiopathic hypercalciuria. *Proc R Soc Med* 46:1077–1081, 1953
59. CALDAS AE, GRAY RW, LEMANN J JR: The simultaneous measurement of vitamin D metabolites in plasma: Studies in healthy adults and in patients with calcium nephrolithiasis. *J Lab Clin Med* 91:840–849, 1978
60. SHEN FH, BAYLINK DJ, NIELSON RL, SHERRARD DJ, IVEY JL, HAUSSLER MR: Increased 1,25-dihydroxyvitamin D in idiopathic hypercalciuria. *J Lab Clin Med* 90:955–962, 1977
61. SUTTON RAL, WALKER VR: Responses to hydrochlorothiazide and acetazolamide in patients with calcium stones: Evidence suggesting a defect in renal tubular function. *N Engl J Med* 302:709–713, 1980
62. BURCKHARDT P, JAEGER P: Secondary hyperparathyroidism in idiopathic renal hypercalciuria: Fact or theory. *J Clin Endocrinol Metab* 53:550–555, 1981
63. COE FL, FAVUS MJ, CROCKETT T, STRAUSS AL, PARKS JH, PORAT A, GANTT CL, SHERWOOD LM: Effects of low calcium diet on urine calcium excretion, parathyroid function and serum $1,25(OH)_2D_3$ levels in patients with idiopathic hypercalciuria and in normal subjects. *Am J Med* 72:25–32, 1982
64. COE FL, CANTERBURY JM, FIRPO JJ, REISS E: Evidence for secondary hyperparathyroidism in idiopathic hypercalciuria. *J Clin Invest* 52:134–142, 1973
65. LAU K, EBY B: Tubular mechanisms for the phosphaturic effects of NH_4Cl administration. *Kidney Int* 19:109, 1981
66. KEMPSON SA: Effect of metabolic acidosis on renal brush border membrane adaptation to low phosphorus diet. *Kidney Int* 22:225–233, 1982
67. TURNER ST, HAUGEN TA, DOUSA TP: Mechanism of phosphaturia induced by glucocorticoids in rats adapted to low phosphate diet. *Clin Res* 29:556A, 1981
68. EBY B, LAU K: Effects of glucagon on tubular PO_4 transport: Contrast with nicotinamide. *Kidney Int* 21:132, 1982
69. JUBIZ W, HAUSSLER MR, MCCAIN TA, TOLMAN KG: Plasma 1,25-dihydroxy-vitamin D levels in patients receiving anticonvulsant drugs. *J Clin Endocrinol Metab* 44:617–621, 1977
70. WARK JD, LARKINS RG, PERRY-KUNE D, PETER CT, ROSS DL, SLOMAN JG: Chronic diphenylhydantoin therapy does not reduce plasma 25-hydroxyvitamin D. *Clin Endocrinol* 11:267–274, 1979
71. HARRISON HC, HARRISON HE: Inhibition of vitamin D stimulated active transport of calcium of rat intestine by diphenylhydantoin phenobarbital treatment. *Proc Soc Exp Biol Med* 153:220–224, 1976
72. HAHN TJ, SCHARP CR, RICHARDSON CA, HALSTEAD LR, KAHN AJ, TEITELBAUM SL: Interaction of diphenylhydantoin and phenobarbital with hormonal mediation of fetal rat bone resorption in vitro. *J Clin Invest* 62:406–414, 1978
73. HAHN TJ, SQUIRES AE, HALSTEAD LR, STROMINGEN DB: Reduced serum 25-hydroxyvitamin D concentration and disordered mineral metabolism in patients with cystic fibrosis. *J Pediatr* 94:38–42, 1979
74. KUKUMOTO Y, TARUI S, TSUKIYAMA K, ICHIHARA K, MORIWAKI K, NONAKA K, MIZUSHIMA T, KOBAYASHI Y, BOKOH S, FUKUNAGA M, MORITA R: Tumor-induced vitamin D-resistant hypophosphatemic osteomalacia associated with proximal renal tubular dysfunction and 1,25-dihydroxyvitamin D deficiency. *J Clin Endocrinol Metab* 49:873–878, 1979
75. BRUNETTE MG, CHABARDES D, IMBERT-TEBOUL M, CLIQUE A, MONTEGUT M, MOREL F: Hormone sensitive adenylate cyclase activity along the nephron of genetically hypophosphatemic mice. *Kidney Int* 15:357–369, 1979